



Baoge QU^{1*}, Hao QU²

¹Department of Gastroenterology, Taishan Hospital, Shandong Province, P. R. China

²Department of Gastroenterology, Yuhuangding Hospital, Yantai city, Shandong 271000, P. R. China

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***Corresponding author:** Baoge QU, Professor, Department of Gastroenterology, Taishan Hospital, Shandong Province, No. 3 Tianwaicun Street, Taiwan City 271000, P. R. China, E-mail: qubaoge@sina.com

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Review Article

Influence of Long-Term Use of Proton Pump Inhibitors on Esophageal and Gastrointestinal Precancerous Lesions or Carcinoma

Abstract

Patients with GERD and Barrett's oesophagus should be encouraged to continue long term use of PPI therapy as a preventive measures for oesophageal adenocarcinoma. However, the conclusions, whether long-term use of PPI may cause FGPs and gastric carcinoma development, remain inconsistent. Now, individual reports showed that long-term treatment with PPI might cause gastric neuroendocrine tumors (g-NETs) and the development of ECL cell carcinoids. Presently enormous study's conclusion supported that long-term use of PPI does not increase in risk of colorectal cancer. Hence, clinical physicians must weigh potential risks of long-term use of PPI against gastrointestinal precancerous lesions or carcinoma.

Introduction

Previously the substantial data on long-term treatment of humans with proton pump inhibitors (PPI) has not revealed any definite risks [1] and prolonged gastric acid suppression with PPI rarely produced adverse event [2]. Hence, Proton pump inhibitors have an excellent safety profile [3], supporting the short-and long-term safety of PPI [4]. They have been become a commonly prescribed class of drugs worldwide [3,5], long-term use of PPI is becoming more prevalent [6]. However, current evidences have demonstrated that long-term use of PPI might generate certain adverse events [3]. Thus, the viewpoints of adverse events for long-term use of proton pump inhibitors in human remain inconsistent. Moreover, studies have shown that chronic acid suppression by proton pump inhibitor therapy might lead to hypergastrinemia [7-9] and increasing enterochromaffin-like cell dysplasia and risk of gastric.

NET development, and progression of carcinogenesis in a certain predisposed subset of Barrett's esophagus patients [9]. However, a contradictory conclusion did not support gastrin dependence of adenocarcinoma of the stomach or the colon and considering that it might be explained by the presence of gastrin receptors of tumour cells and the role of gastrin as an autocrine growth factor in some of these tumours [10]. Additionally, a study suggested that prolonged hypochlorhydria predisposed to gastric carcinoma by an increase in the production of carcinogenic N-nitroso compounds [11].

However, accumulated evidence [12], has shown that gastrin likely does not promote-and may even suppress-distal antral gastric cancer. Hence, these hypotheses have led to concerns about the safety of long-term PPI administration [11,13]. Particularly, whether long-term use of proton pump inhibitors in human might result in esophageal and gastrointestinal precancerous lesions or carcinoma causes the extensive concern in the clinical.

1. The associations between long-term uses of proton pump inhibitors and Barrett's esophagus, esophageal cancerGastroesophageal reflux disease (GERD) is a risk factor for the development of Barrett's esophagus and esophageal adenocarcinoma. Current evidences have confirmed that long-term use of PPI seems to be a safe and efficient treatment for GERD [14,15] and Barrett's oesophagus [16]. Long-term acid suppression reduced proliferation in Barrett's esophagus samples [17] and may reduce esophageal adenocarcinoma (EAC) by a minimum of 19% [18]. Use of ongoing PPI therapy appeared beneficial in the prevention of dysplasia and adenocarcinoma in patients with Barrett's oesophagus [19]. Although PPI treatment over 1-13 years did not shorten the Barrett's oesophagus segment but squamous islands appeared in many patients, and, the incidence of oesophageal adenocarcinoma received proton pump inhibitor-treated patients was low [20]. Hence, PPI use was associated with a decreased incidence of neoplasia in Barrett's esophagus [21], supporting a cancer-protective role for PPI in patients with Barrett's esophagus

[22]. However, an opposite study result revealed that PPI did not present the cancer-protective effects [23]. We summarize the above results, reconsidering that patients with GERD and Barrett's oesophagus should be encouraged to continue long term use of PPI therapy as a preventive measures for oesophageal adenocarcinoma.

2. The association between long-term uses of proton pump inhibitors and polyps, gastric carcinoma, gastric neuroendocrine tumors

Gland Polyps (FGPs) is an important precancerous lesions of gastric carcinoma. Whether long-term use of PPI might increase or decrease the a incidence of denoma remains no consistent conclusion .Studies have revealed that long-term use of PPI was a particularly strong risk factor [24,25]. Among them, PPI have been linked to gastric fundal polyposis and not antral gland polyposis [26]. Another report originating from an Asian country showed that fundal Gland Polyps (FGPs) in the corpus of stomach were significantly higher than the fundus in a patient of long-term PPI therapy [27]. There was a possible causal relation between the use of omeprazole and the development of fundic gland polyps in patients without H. pylori gastritis [28].

Gastric polyps and nodules might be found in children receiving longterm omeprazole therapy during the mean observation period of 31 months [29]. Long-term use of proton pump inhibitors may be associated with the presence of small gastric fundic gland polyps and hyperplastic polyps [30]. But, the opposite research results showed that sporadic FGPs may not be induced by PPI therapy [31]. For instance, the prevalence of FGPs and polyps number were not link with omeprazole therapy [32]. Furthermore, longterm use of PPI did not influence the frequency, growth, or histology of adenomatous polyps [33]. Long-term use of PPI was associated with a reduction in both baseline and interval development of hyperplastic polyps [33]. Hence, whether long-term use of PPI might casuse FGPs is inconsistent, it still need to further confirme that whether there are the associations between long-term use of PPI and FGPs.

Whether long-term use of PPI might result in gastric carcinoma development remains controversial. Long-term use of PPI was related to increased risk of gastric cancer [34], via stimulation of DNA-damaged cells; and, increased risk of periampullary cancers [35], via long-lasting iatrogenic hypergastrinemia induced by potent inhibitors of acid secretion. Additionally, human gastric carcinomas of diffuse type, particularly the signet-ring subtype, showed ECL cell differentiation, suggesting involvement of gastrin in the carcinogenesis [36]. However, recent study indicated no association between PPI use and the risk of gastric cancers [8]. There are tremendous reports does not support the above viewpoints, which long-term inhibition of the gastric proton pump did not increase the risk of gastric cancer because of antioxidant depletion [37]; there are no evidence that pantoprazole as a longer acting PPI conferred an excess risk of gastric cancer, other gastrointestinal cancers or all cancers compared with other shorter-acting PPI [38]. There has even

study suggested that anti-carcinogenic actions of PPI were augmented with PPI-induced hypergastrinemia [39]. But, Recently a multicenter study confirmed that elevated lesions and cobblestone-like mucosa were characteristic endoscopic features in PPI users. And ,a gender-associated difference was noted in terms of the frequency of these lesions [40]; another study results [41], pointed to a major influence of reverse causation and confounding by indication on the association between PPI use and gastric cancer incidence, the finding of increased incidence among PPI users with most prescriptions and longest follow-up warrants further investigation. In addition, PPI intake was associated with the existence and epidemiological relevance of gastric neuroendocrine tumors (g-NETs) [42,43], illustrating a patient with a poorly differentiated neuroendocrine carcinoma with ECL cell characteristics probably induced by hypergastrinemia secondary to long-term use of PPI [42]. There were reports indicating development of ECL cell carcinoids after long-term treatment with proton pump inhibitors [43] and hypergastrinemia secondary to PPI treatment might induce enterochromaffin-like cell carcinoids in man [44,45]. Additionally, based on few case reports showed although PPI-induced hypergastrinaemia has the potential to stimulate hyperplasia of enterochromaffin-like (ECL) cells,however, the role was very weak , considering Physicians have to continue PPI prescription without any fear about the occurrence of this adverse event [46]. However, Children with long-termuse of PPI did not appear to develop atrophic gastritis or carcinoid tumours [47]. In short, whether long-term use of PPI might result in gastric carcinoma development and carcinoid tumours need to be verified by large prospective studies.

3. The association between long-term uses of proton pump inhibitors and colorectal cancer,

Enormous researches have indicated no association between long-term use of PPI at a regular dose and the increase in risk of colorectal cancer [8,48-52]. However, only a previously study suggested that PPI use might be modestly associated with CRC risk [53,54]. According to the results of the present majority studies, the conclusion seem to support the opinions, which long-term use of PPI does not increase in risk of colorectal cancer. Further research should needed to confirm the lock of a risk-increasing effect of long-term us of PPI.

Conclusion

Patients with GERD and Barrett's oesophagus should be encouraged to continue long term use of PPI therapy as a preventive measures for oesophageal adenocarcinoma. However. whether long-term use of PPI may casuse FGPs and gastric carcinoma development remains are inconsistent. long-term treatment with PPI might cause gastric neuroendocrine tumors (g-NETs) and the development of ECL cell carcinoids. The presently study's conclusion seem to support that long-term use of PPI does not increase in risk of colorectal cancer. Hence, Physicians must weigh potential risks of long-term use of PPI against therapeutic benefit. The continued follow-up of patients taking PPI for extended periods will provide greater experience regarding the potential gastrointestinal adverse effects of long-term acid suppression.

References

- Yeomans ND, Dent J (2000) Personal review: alarmism or legitimate concerns about long-term suppression of gastric acid secretion? *Aliment Pharmacol Ther* 14: 267-271. [Link: https://goo.gl/TQ2a1l](https://goo.gl/TQ2a1l)
- Laine L, Ahnen D, McClain C, Solcia E, Walsh JH (2014) Review article: potential gastrointestinal effects of long-term acid suppression with proton pump inhibitors. *Aliment Pharmacol Ther* 14: 651-668. [Link: https://goo.gl/1nNH5k](https://goo.gl/1nNH5k)
- Sheen E, Triadafilopoulos G (2011) Adverse effects of long-term proton pump inhibitor therapy. *Dig Dis Sci* 56: 931-950. [Link: https://goo.gl/eSpHkZ](https://goo.gl/eSpHkZ)
- Garnett WR (1998) Considerations for long-term use of proton-pump inhibitors. *Am J Health Syst Pharm* 55: 2268-2279. [Link: https://goo.gl/bYJwTg](https://goo.gl/bYJwTg)
- Ali T, Roberts DN, Tierney WM (2009) Long-term safety concerns with proton pump inhibitors. *Am J Med* 122: 896-903. [Link: https://goo.gl/CftYwD](https://goo.gl/CftYwD)
- Roulet L, Vernaz N, Giostra E, Gasche Y, Desmeules J (2012) Adverse effects of proton pump inhibitors: should we worry about long-term exposure? *Rev Med Interne* 33: 439-445. [Link: https://goo.gl/ysbUVv](https://goo.gl/ysbUVv)
- McCloy RF, Arnold R, Bardhan KD, Cattan D, Klinkenberg-Knol E, et al. (1995) Pathophysiological effects of long-term acid suppression in man. *Dig Dis Sci* 40: 96S-120S. [Link: https://goo.gl/NKtU06](https://goo.gl/NKtU06)
- Mathieu N (2008) Risk of long-term treatment with proton pump inhibitors. *Rev Prat* 58: 1451-1454. [Link: https://goo.gl/GppzEh](https://goo.gl/GppzEh)
- Ko Y, Tang J, Sanagapalli S, Kim BS, Leong RW (2016) Safety of proton pump inhibitors and risk of gastric cancers: review of literature and pathophysiological mechanisms. *Expert Opin Drug Saf* 15: 53-63. [Link: https://goo.gl/nzxMr7](https://goo.gl/nzxMr7)
- Creutzfeldt W, Lamberts R (1991) Is hypergastrinaemia dangerous to man? *Scand J Gastroenterol Suppl* 180: 179-191. [Link: https://goo.gl/7t2SOJ](https://goo.gl/7t2SOJ)
- Moncur PH, Heatley RV (2000) Safety of proton-pump inhibitors: the acid test. *Eur J Gastroenterol Hepatol* 12: 145-147. [Link: https://goo.gl/j4EKuv](https://goo.gl/j4EKuv)
- Hayakawa Y, Chang W, Jin G, Wang TC (2006) Gastrin and upper GI cancers. *Curr Opin Pharmacol* 31: 31-37. [Link: https://goo.gl/T0XVd6](https://goo.gl/T0XVd6)
- McCarthy DM (2010) Adverse effects of proton pump inhibitor drugs: clues and conclusions. *Curr Opin Gastroenterol* 26: 624-63. [Link: https://goo.gl/Rf6lcb](https://goo.gl/Rf6lcb)
- Pohle T, Domschke W (2000) Results of short-and long-term medical treatment of gastroesophageal reflux disease (GERD). *Langenbecks Arch Surg* 385: 317-323. [Link: https://goo.gl/F07FrZ](https://goo.gl/F07FrZ)
- Lada MJ, Nieman DR, Han M, Timratana P, Alsalahi O, et al. (2013) Gastroesophageal reflux disease, proton-pump inhibitor use and Barrett's esophagus in esophageal adenocarcinoma: Trends revisited. *Surgery* 154: 856-864. [Link: https://goo.gl/Hn59GL](https://goo.gl/Hn59GL)
- Obszynska JA, Atherfold PA, Nanji M, Glancy D, Santander S, et al. (2010) Long-term proton pump induced hypergastrinaemia does induce lineage-specific restitution but not clonal expansion in benign Barrett's esophagus in vivo. *Gut* 59: 156-163. [Link: https://goo.gl/6TpvZI](https://goo.gl/6TpvZI)
- Lao-Sirieix P, Roy A, Worrall C, Vowler SL, Gardiner S, et al. (2006) Effect of acid suppression on molecular predictors for esophageal cancer. *Cancer Epidemiol Biomarkers Prev* 15: 288-293. [Link: https://goo.gl/iHEUK3](https://goo.gl/iHEUK3)
- Sharaiha RZ, Freedberg DE, Abrams JA, Wang YC (2014) Cost-effectiveness of chemoprevention with proton pump inhibitors in Barrett's esophagus. *Dig Dis Sci* 59: 1222-1230. [Link: https://goo.gl/8zwpFV](https://goo.gl/8zwpFV)
- Hillman LC, Chiragakis L, Shadbolt B, Kaye GL, Clarke AC (2004) Proton-pump inhibitor therapy and the development of dysplasia in patients with Barrett's esophagus. *Med J Aust* 180: 387-391. [Link: https://goo.gl/CCnHkB](https://goo.gl/CCnHkB)
- Cooper BT, Chapman W, Neumann CS, Gearty JC (2006) Continuous treatment of Barrett's esophagus patients with proton pump inhibitors up to 13 years: observations on regression and cancer incidence. *Aliment Pharmacol Ther* 23: 727-733. [Link: https://goo.gl/46UqnJ](https://goo.gl/46UqnJ)
- Spechler SJ (2014) Does Barrett's esophagus regress after surgery (or proton pump inhibitors)? *Dig Dis* 32: 156-163. [Link: https://goo.gl/7bXeUX](https://goo.gl/7bXeUX)
- Dunbar KB, Souza RF, Spechler SJ (2015) The Effect of Proton Pump Inhibitors on Barrett's Esophagus. *Gastroenterol Clin North Am* 44: 415-424. [Link: https://goo.gl/gepldJ](https://goo.gl/gepldJ)
- Hvid-Jensen F, Pedersen L, Funch-Jensen P, Drewes AM (2014) Proton pump inhibitor use may not prevent high-grade dysplasia and oesophageal adenocarcinoma in Barrett's esophagus: a nationwide study of 9883 patients. *Aliment Pharmacol Ther* 39: 984-991. [Link: https://goo.gl/wEk7CU](https://goo.gl/wEk7CU)
- Huang CZ, Lai RX, Mai L, Zhou HL, Chen HJ, et al. (2014) Relative risk factors associated with the development of fundic gland polyps. *Eur J Gastro-enterol Hepatol* 26: 1217-1221. [Link: https://goo.gl/27VNXN](https://goo.gl/27VNXN)
- Zelter A, Fernández JL, Bilder C, Rodríguez P, Wonaga A, et al. (2011) Fundic gland polyps and association with proton pump inhibitor intake: a prospective study in 1,780 endoscopies. *Dig Dis Sci* 56: 1743-1748. [Link: https://goo.gl/bhgl1H](https://goo.gl/bhgl1H)
- Alqutub AN, Masoodi I (2010) A case of gastric polyposis in antral area of stomach following prolonged proton-pump therapy. *Ger Med Sci* 8: 19. [Link: https://goo.gl/Dd68s3](https://goo.gl/Dd68s3)
- Yakoob J, Abbas Z, Jafri W, Ahmad Z (2008) Gastric corpus polyps associated with Proton Pump Inhibitors therapy. *J Coll Physicians Surg Pak* 18: 172-173. [Link: https://goo.gl/noosJ5](https://goo.gl/noosJ5)
- el-Zimaity HM, Jackson FW, Graham DY (1997) Fundic gland polyps developing during omeprazole therapy. *Am J Gastroenterol* 92: 1858-1860. [Link: https://goo.gl/ezHUD6](https://goo.gl/ezHUD6)
- Pashankar DS, Israel DM (2002) Gastric polyps and nodules in children receiving long-term omeprazole therapy. *J Pediatr Gastroenterol Nutr* 35: 658-662. [Link: https://goo.gl/wzuRGU](https://goo.gl/wzuRGU)
- Choudhry U, Boyce HW Jr, Coppola D (1998) Proton pump inhibitor-associated gastric polyps: a retrospective analysis of their frequency, and endoscopic, histologic, and ultrastructural characteristics. *Am J Clin Pathol* 110: 615-621. [Link: https://goo.gl/iRrMDz](https://goo.gl/iRrMDz)
- Cao H, Qu R, Zhang Z, Kong X, Wang S, et al. (2014) Sporadic fundic gland polyps are not associated with proton pump inhibitors therapy but negatively correlate with *Helicobacter pylori* infection in China. *Chin Med J* 127: 1239-1243. [Link: https://goo.gl/XoHHwv](https://goo.gl/XoHHwv)
- Declich P, Tavani E, Ferrara A, Caruso S, Bellone S (2005) Sporadic fundic gland polyps: clinico-pathologic features and associated diseases. *Pol J Pathol* 56: 131-137. [Link: https://goo.gl/EZ7TSR](https://goo.gl/EZ7TSR)
- Singh M, Dhindsa G, Friedland S, Triadafilopoulos G (2007) Long-term use of proton pump inhibitors does not affect the frequency, growth, or histologic characteristics of colon adenomas. *Aliment Pharmacol Ther* 26: 1051-1061. [Link: https://goo.gl/6JVgJB](https://goo.gl/6JVgJB)
- Waldum HL, Gustafsson B, Fossmark R, Qvigstad G (2005) Antiulcer drugs and gastric cancer. *Dig Dis Sci* 50: S39-44. [Link: https://goo.gl/BLak8d](https://goo.gl/BLak8d)
- Chien LN, Huang YJ, Shao YH, Chang CJ, Chuang MT, et al. (2016) Proton pump inhibitors and risk of periampullary cancers—A nested case-control study. *Int J Cancer* 138: 1401-1409. [Link: https://goo.gl/avvpeK](https://goo.gl/avvpeK)

36. Waldum HL, Hauso Ø, Fossmark R (2014) The regulation of gastric acid secretion - clinical perspectives. *Acta Physiol (Oxf)* 210: 239-256. [Link: https://goo.gl/BkzuwA](https://goo.gl/BkzuwA)
37. White KL, Chalmers DM, Martin IG, Everett SM, Neville PM, et al. (2002) Dietary antioxidants and DNA damage in patients on long-term acid-suppression therapy: a randomized controlled study. *Br J Nutr* 88: 265-271. [Link: https://goo.gl/epf4zI](https://goo.gl/epf4zI)
38. Schneider JL, Kolitsopoulos F, Corley DA (2016) Risk of gastric cancer, gastrointestinal cancers and other cancers: a comparison of treatment with pantoprazole and other proton pump inhibitors. *Aliment Pharmacol Ther* 43: 73-82. [Link: https://goo.gl/YRRv7H](https://goo.gl/YRRv7H)
39. Han YM, Park JM, Kangwan N, Jeong M, Lee S, et al. (2015) Role of proton pump inhibitors in preventing hypergastrinemia-associated carcinogenesis and in antagonizing the trophic effect of gastrin. *J Physiol Pharmacol* 66: 159-167. [Link: https://goo.gl/bS9BgP](https://goo.gl/bS9BgP)
40. Kiso M, Ito M, Boda T, Kotachi T, Masuda K, et al. (2017) Endoscopic findings of the gastric mucosa during long-term use of proton pump inhibitor - a multicenter study. *Scand J Gastroenterol* 9: 1-5. [Link: https://goo.gl/nkrbDt](https://goo.gl/nkrbDt)
41. Poulsen AH, Christensen S, McLaughlin JK, Thomsen RW, Sørensen HT, et al. (2009) Proton pump inhibitors and risk of gastric cancer: a population-based cohort study. *Br J Cancer* 100: 1503-1507. [Link: https://goo.gl/pPYGTt](https://goo.gl/pPYGTt)
42. Jianu CS, Lange OJ, Viset T, Qvigstad G, Martinsen TC, et al. (2012) Carcinoma after long-term use of proton pump inhibitor. *Scand J Gastroenterol* 47: 64-67. [Link: https://goo.gl/hqAlzT](https://goo.gl/hqAlzT)
43. Cavalcoti F, Zilli A, Conte D, Ciafardini C, Massironi S (2015) Gastric neuroendocrine neoplasms and proton pump inhibitors: fact or coincidence? *Scand J Gastroenterol* 50: 1397-1403. [Link: https://goo.gl/CHBV2E](https://goo.gl/CHBV2E)
44. García Rodríguez LA, Lagergren J, Lindblad M (2006) Gastric acid suppression and risk of oesophageal and gastric adenocarcinoma: a nested case control study in the UK. *Gut* 55: 1538-1544. [Link: https://goo.gl/zwnWkw](https://goo.gl/zwnWkw)
45. Jianu CS, Fossmark R, Viset T, Qvigstad G, Sørđal O, et al. (2012) Gastric carcinoids after long-term use of a proton pump inhibitor. *Aliment Pharmacol Ther* 36: 644-649. [Link: https://goo.gl/vWg1J0](https://goo.gl/vWg1J0)
46. Jianu CS, Fossmark R, Viset T, Qvigstad G, Sørđal O, et al. (2012) Gastric carcinoids after long-term use of a proton pump inhibitor. *Aliment Pharmacol Ther* 36: 644-649. [Link: https://goo.gl/vWg1J0](https://goo.gl/vWg1J0)
47. Savarino V, Dulbecco P, Savarino E (2016) Are proton pump inhibitors really so dangerous? *Dig Liver Dis* 48: 851-859. [Link: https://goo.gl/fOVrVV](https://goo.gl/fOVrVV)
48. Hassall E, Owen D, Kerr W, Sturby T, Richardson P, et al. (2011) Gastric histology in children treated with proton pump inhibitors long term, with emphasis on enterochromaffin cell-like hyperplasia. *Aliment Pharmacol Ther* 33: 829-836. [Link: https://goo.gl/pFKMx6](https://goo.gl/pFKMx6)
49. Freeman HJ (2008) Proton pump inhibitors and an emerging epidemic of gastric fundic gland polyposis. *World J Gastroenterol* 14: 1318-1320. [Link: https://goo.gl/5qlen7](https://goo.gl/5qlen7)
50. Robertson DJ, Larsson H, Friis S, Pedersen L, Baron JA, et al. (2007) Proton pump inhibitor use and risk of colorectal cancer: a population-based, case-control study. *Gastroenterology* 133: 755-760. [Link: https://goo.gl/CsgzSz](https://goo.gl/CsgzSz)
51. Freeman HJ (2008) Proton pump inhibitors and an emerging epidemic of gastric fundic gland polyposis. *World J Gastroenterol* 14: 1318-1320. [Link: https://goo.gl/mIDYVF](https://goo.gl/mIDYVF)
52. van Soest EM, van Rossum LG, Dieleman JP, van Oijen MG, Siersema PD, et al. (2008) Proton pump inhibitors and the risk of colorectal cancer. *Am J Gastroenterol* 103: 966-973. [Link: https://goo.gl/aTyZf0](https://goo.gl/aTyZf0)
53. Yang YX, Hennessy S, Propert K, Hwang WT, Sedarat A, et al. (2007) Chronic proton pump inhibitor therapy and the risk of colorectal cancer. *Gastroenterology* 133: 748-754. [Link: https://goo.gl/zD6HRM](https://goo.gl/zD6HRM)
54. Chubak J, Boudreau DM, Rulyak SJ, Mandelson MT (2009) Colorectal cancer risk in relation to use of acid suppressive medications. *Pharmacoepidemiol Drug Saf* 18: 540-544. [Link: https://goo.gl/53bCxZ](https://goo.gl/53bCxZ)